Cell-Based Delivery of Chemotherapeutics and Antibiotics

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Cell-based delivery systems have the potential to effectively treat localized damaged tissue including solid tumors and sites of bacterial infection. Defensive cells (neutrophils and monocytes) are known to migrate to tumors and can be used as vehicles for targeted delivery. Additionally, defensive cells actively detect and consume bacteria efficiently including the non-pathogenic bacterium, Micrococcus luteus. M. luteus can be loaded with chemotherapeutics or antibiotics prior to uptake by defensive cells. The resulting cell-delivery system is a defensive cell containing drug loaded M. luteus and Fe/Fe₃O₄ nanoparticles that travels to the inflamed site and releases the drugs in response to an alternating current magnetic field. Here drug uptake and retention in M. luteus will be presented.

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A New Approach Towards Predicting the Outcome of Treating TripleNegative Cancer (2013 Project)

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Triple-negative breast cancer (TNBC) comprises any breast cancer that is not characterized by expression of the estrogen receptor (ER), progesterone receptor (PR) or Human Epidermal Growth Factor Receptor 2 (Her2/neu).¹ This is a very heterogeneous group of cancers, which accounts for up to 25% of all breast cancer cases in the US. Although 50% to 75% of all basaltype breast cancers are triple-negative, there is no standard protocol to identify them as of yet.¹ Many TNBCs react well to (aggressive) chemotherapy, whereas others do not. It is of importance for the development of a new standard of care that TNBC is clearly NOT a homogeneous group. Great differences in response to treatment and relapse pattern are observed, with respect to the ER, PR-, and Her2/neu-expressing cancers.² Therefore, it would be highly advantageous to develop analytical methods to distinguish subgroups of TNBCs.

Matrix Metalloproteinases (MMPs) are a family of zinc containing endopeptidases. They are synthesized as inactive zymogens or proMMPs, which will later be activated by serine
proteases or other MMPs. MMPs degrade the proteins that make up the extracellular matrix (ECM) and the basement membrane (BM). Interestingly, the major producer of the MMP’s are the stromal cells surrounding the tumor. MMPs are vital to cancer survival and progression for several reasons – they cleave cell surface bound growth factors from the stromal and epithelial cells and release them to interact with the cancer cells to stimulate growth, and they play a role in angiogenesis by releasing pro-angiogenic factors and starting pro-angiogenic protease cascades. I have measured the activity of MMP-11 and MMP-13 in the blood serum of a group of 20 women who have been diagnosed with TNBC using the nanoplatforms for protease detection that have been developed by Dr. Stefan Bossmann and Dr. Deryl L. Troyer. The samples have been provided by Priyanka Sharma, MD, Hematology and Oncology, The University of Kansas Hospital.

Gli1 is an established oncogene that is expressed in TNBC. It enhances migration and invasion via up-regulation of MMP-11. There is an emerging paradigm in the recent literature that some of the same factors that drive epithelial–mesenchymal transition (EMT) upregulate MMP13 expression (e.g., TGFb, IL1b, TNFa), indicating an association of MMP13 with invasion and metastasis. MMP-11 and MMP-13 can be detected using fluorescence-based assays within 60min. The MMP-activities will be compared with the complete histology of the TNBCs that will be performed by Dr. Sharma. The goal of this study is to verify/falsify these two pathways in patient-specific TNBC pathology, with the goal of developing better predictors for cancer treatment and survival.

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**Synthesizing Magnetic Nanoparticles for Hyperthermia Treatment of Cancer**

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The scientific community has cultivated various ideas for the detection and treatment of cancer. The latter is often described as the overproduction of abnormal cells, but cancer biology is much more complex. The best model is to understand tumors in analogy to sophisticated organs. Various methods, such as surgery and chemotherapy have been utilized to eliminate tumors, but have been often ineffective due to the high resistance of the cancer. A/C magnetic hyperthermia mediated with magnetic nanoparticles (MNP) has the ability to precisely deliver prodrugs, such as Fe/Fe₃O₄ MNP bound SN38 to the cancer site. Therefore, the union of chemotherapy with A/C magnetic hyperthermia (AMF), called thermochemotherapy, is a novel and promising treatment approach.
Enhanced delivery of chemotherapeutic drugs to the tumor site decreases the amount of drug required. Hyperthermia is able to activate the immune system against cancer. I have studied the SAR capacities of cubical and spherical nanoparticles. The different morphological nanoparticles exhibited different heating capacities as indicated by their Specific Absorption Rates (SAR, measured in J g(Fe)\(^{-1}\)). We are aiming at SAR > 500 J g\(^{-1}\), which will permit short heating cycles (10 min). Furthermore, enhanced delivery of chemotherapeutic drugs to the tumor site decreases the amount of drug required and the amount of nanoparticles required for treating a patient can be reduced to < 5g per cancer treatment.

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**Protease Detection Through Nanoparticles for Early Cancer Diagnosis**

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Fluorescence-based assays offer an inexpensive, simple, and sensitive way to measure the reactivity of proteases. Proteases, such as matrix metalloproteinases (MMP’s) and urokinase plasminogen activator (uPA), are enzymes that cleave other proteins and speed up biological processes in the human body. It is known that MMP’s and uPA are necessary for the survival of cancer cells and are therefore overexpressed in these cells. By measuring the activity of MMP’s and uPA in cancer cells, one can use these proteases as a biomarker for the diagnosis of breast cancer and assure an early and correct diagnosis. One way to measure MMP and uPA activity is by the use of nanoparticles. By using an Fe/Fe\(_3\)O\(_4\) nanoparticle as a nanoplatform specific to each MMP and uPA, the fluorescence resulting from the cleaved consensus sequences of cyanine dyes and porphyrins results in detection as sensitive as down to 1*10\(^{-16}\) mol l\(^{-1}\). I have measured the fluorescence of MMP-11, MMP-3, MMP-9 and uPA in blood serum and tissue samples of breast cancer patients. To prepare the assay, I add 75 microliters of the nanoparticle solution to 3mL of the assay compound and 30 microliters of either the blood serum or tissue sample. A 60 minute incubation period suffices to obtain reliable results for the activity of MMP-11 and uPA. The purpose of this research is to determine the fluorescence increase of the MMP’s and uPA and also to determine the disparity of the fluorescence increase among the proteases studied.